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SYNTHESIS OF 3-CARBOXY-20-KETO STEROID, SB 209963, A 5α-REDUCTASE INHIBITOR, BY PALLADIUM-CATALYZED HYDROXYCARBONYLATION

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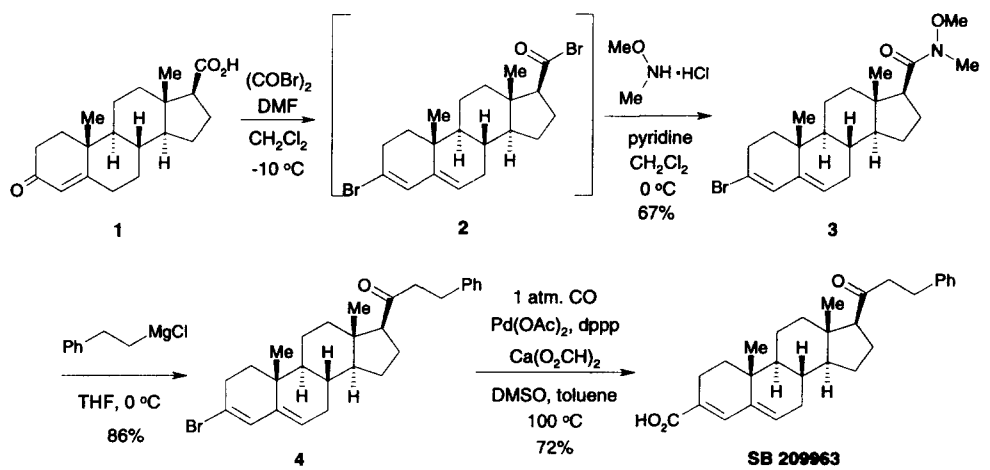
Abstract: SB 209963 was produced in three steps starting from 17β-carboxyandrost-4-en-3-one. A palladium-catalyzed hydroxycarbonylation introduced the carboxylic acid under mild conditions without epimerization at C-17. This reaction represents the first example of hydroxycarbonylation of a vinyl halide under neutral conditions.

The potential treatment of several disorders, including benign prostatic hypertrophy and male pattern baldness, through the use of steroid 5α-reductase(SR) inhibitors[1] has brought renewed interest in the synthesis of the steroidal compounds. One such compound is the ketosteroidal acid SB 209963. Previous syntheses introduced the ketone functionality through addition of the appropriate Grignard either to an aldehyde at C-20 or the corresponding 2-thiopyridyl ester[2]. The carboxylic acid moiety in these routes was first reduced to an alcohol, then later reoxidized to the desired acid. A more direct synthesis of SB 209963 was attempted by introduction of the carboxylic acid by Pd-catalyzed alkoxycarbonylation followed by hydrolysis to the acid using conditions(K_2CO_3 in MeOH:H_2O) which had been previously reported for the analogous C-20 carboxamides.[3] This approach, however, resulted in unacceptable amounts(10-20%) of epimerization at C-17 during the basic hydrolysis to the acid. A new synthesis that avoided this problem and also shortened the synthesis to three steps is now reported. The key reaction is the first application of a Pd-catalyzed hydroxycarbonylation of a bromodiene.

Scheme 1



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The synthesis, shown in Scheme 1, begins with reaction of commercially available 17β-carboxyandrost-4-en-3-one, **1**, with 2.2 eq. of Vilsmeier reagent formed from oxalyl bromide and DMF. This produces not only the acid halide at C-20, but also the bromodiene in rings A and B. An inverse quench of **2** into a CH_2Cl_2 solution of methoxymethylamine hydrochloride and pyridine forms Weinreb amide **3**.[4] The reaction of **3** with phenethylmagnesium chloride then smoothly gives ketone **4** in 86% yield. The addition of Grignard reagents to convert C-20 amides to ketones has been reported in azasteroids.[5] To complete the synthesis, a direct method by which the acid functionality could be introduced was desired. Examination of the literature revealed that while the Pd-catalyzed hydroxycarbonylation of aryl halides[6] and aryl triflates[7] under neutral conditions has been reported, the same reaction had not been extended to alkenyl halides. Reaction of **4** with 2 mol% $Pd(OAc)_2$, 2 mol% dppp, and 0.6 equivalents calcium formate in 2:1 DMSO:toluene under 1 atm CO gave SB 209963 in 72% yield.[8] No evidence of epimerization at C-17 was observed. The synthesis described produced SB 209963 in three steps with no chromatographic separations and has produced quatities in the decagram range. The hydroxycarbonylation used is especially noteworthy since it increases the scope of the methodology to vinyl bromides and demonstrates its ability to introduce in a single step a carboxylic acid in the presence of an epimerizable center.

Notes and References:

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8. Preparation of SB 209963: Bromodiene **4** (24.76 g, 57 mmol) was dissolved in 200 mL DMSO and 100 mL of toluene. The solutions was then heated to 80° C and saturated with CO by bubbling CO for 30 min. $Pd(OAc)_2$ (254 mg, 1.14 mmol, 2 mol%), dppp (470 mg, 1.14 mmol, 2 mol%), and calcium formate(4.44 g, 34.2 mmol, 0.6 eq.) were added. The mixture was stirred at 80° C while kept under 1 atm CO. After 20h the reaction was complete as seen by disappearence of **4** by HPLC. The mixture was cooled to r.t., diluted with EtOAc(1600 mL) and washed with 1N HCl(2 x 600 mL). The organic layer was filtered through Celite and the filtrate rotary evaporated to ~200 mL total volume at which point crystallization was observed. The mixture was allowed stirred at 0° C for 2h to complete crystallization. The solid was collected and dried in vacuo to give SB 209963 as an off-white solid. Yield = 16.72g(72%).